

Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis

A. M. WILSON, L. C. ORR, E. J. SIMS and B. J. LIPWORTH

Asthma & Allergy Research Group, Department of Clinical Pharmacology & Therapeutics, Ninewells Hospital & Medical School, University of Dundee, Dundee, Scotland

Summary

Background The combination of a leukotriene receptor antagonist with an antihistamine may have beneficial effects in seasonal allergic rhinitis (SAR).

Objective To determine how combined oral mediator blockade compares to monotherapy with intranasal corticosteroid in the treatment of SAR.

Methods Twenty-two patients with seasonal allergic rhinitis were enrolled in a placebo controlled crossover study comparing 2 weeks therapy of either (a) 200 µg intranasal mometasone furoate (MF) once daily or (b) 10 mg oral montelukast plus 10 mg oral cetirizine once daily (MON/CZ), with a 7–10 day placebo period prior to each treatment period. Domiciliary measures of symptoms and nasal flow were recorded daily. Measurements of posterior rhinomanometry, acoustic rhinometry and nasal nitric oxide were made after all treatment and placebo periods.

Results There were significant ($P < 0.05$) improvements in domiciliary peak nasal flow (l/min) with both MF (133 (3.8)) and MON/CZ (124 (3.8)) compared to pooled placebo (110 (4.0)). Both treatments also showed significant improvement in terms of nasal blockage (units) (PL: 1.1(0.1), MF: 0.5 (0.1), MON/CZ 0.7 (0.1); and total nasal symptoms (units) (PL: 3.5 (0.3), MF 1.6 (0.3), MON/CZ 1.7 (0.3)), although there was no significant difference between the two active treatments. There were no significant differences between placebo and treatment for rhinomanometry, acoustic rhinometry or nitric oxide.

Conclusions Both intranasal mometasone furoate as monotherapy and oral cetirizine plus montelukast as cotherapy were equally effective for objective and subjective measures of treatment response in SAR. Domiciliary measurements of symptoms and peak flow were more sensitive than laboratory measurements of rhinomanometry, acoustic rhinometry and nasal nitric oxide.

Keywords: allergic rhinitis, corticosteroid, leukotriene antagonist, antihistamine, mometasone furoate

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Introduction

Allergic rhinitis is a common condition, with increasing prevalence, occurring in up to 20% of the population [1]. Although the condition does not result in hospitalization or

mortality, it is distressing to patients and may result in absenteeism from work or schooling. Topically delivered intranasal corticosteroids are widely recognized to be the first-line anti-inflammatory treatment for allergic rhinitis, as reflected in current guidelines [2]. They exert their anti-inflammatory activity in a non-selective way by affecting a wide range of inflammatory and structural cells.

Histamine and cysteinyl leukotrienes are important

Correspondence: B.J. Lipworth, Asthma & Allergy Research Group, Department of Clinical Pharmacology & Therapeutics, Ninewells Hospital & Medical School, University of Dundee, Dundee DD1 9SY, Scotland.

inflammatory mediators in the pathogenesis of allergic rhinitis [3–5]. Their effects can now be blocked specifically by selective histamine and leukotriene receptor antagonists, respectively. Although they are not currently licensed for the treatment of allergic rhinitis, studies have shown clinical efficacy with leukotriene receptor antagonists [6] [7]; and in the future will be regarded as a therapeutic option [8]. However, they have been shown to be less efficacious than intranasal corticosteroids. For example, zafirlukast as monotherapy has been shown to be inferior to intranasal beclomethasone dipropionate on nasal symptoms and biopsy [9], and intranasal budesonide to be superior to montelukast in terms of nasal flow, symptoms and nitric oxide [10]. Histamine receptor antagonists, although accepted as standard therapy for seasonal allergic rhinitis [11], tend to be less efficacious than intranasal corticosteroids [12] [13], particularly for nasal blockage [14].

For any treatment to be effective in allergic rhinitis, it should be able to attenuate the early as well as late phase allergen reaction; the latter is thought to be due to influx of airway inflammatory cells. In this respect, leukotriene receptor antagonists have been shown to attenuate the late allergic response [15–17]. Moreover, Roquet *et al* [18] have shown that both the early and late phase allergic response can be markedly reduced by the combination of loratadine and zafirlukast to a greater degree than with either alone.

Cetirizine is particularly effective at controlling patients' nasal itch and sneezing, as it is an antagonist at histamine H₁ receptors, but is relatively less effective at relieving symptoms of nasal blockage. Montelukast, on the other hand, is an antagonist at CysLT₁ receptors and therefore attenuates the leukotriene-induced effects of increased vascular permeability and oedema resulting in control of nasal blockage. By combining both receptor antagonists, all of the symptoms of allergic rhinitis may be alleviated.

The hypothesis being addressed in the study is that by combining specific mediator antagonists, histamine and leukotriene receptor antagonists, it may be possible to attenuate the allergic inflammatory response of allergic rhinitis. The clinical effects of the current first-line therapy for allergic rhinitis, intranasal corticosteroids, will therefore be compared to histamine and leukotriene receptor blockade.

Patients

Twenty-two patients, mean (SE) age 35 (13.1) years, with symptomatic seasonal allergic rhinitis according to current criteria [2], were recruited to completion. Prior to enrolling in the study, seven were taking intranasal corticosteroids (beclomethasone 200 µg bid *n* = 6, triamcinolone acetonide

200 µg/day *n* = 1) and 14 were taking oral antihistamines (cetirizine 10 mg/day *n* = 6, loratadine 10 mg/day *n* = 4, terfenadine 60 mg bid *n* = 3, chlorpheniramine 4 mg qid *n* = 1). No patients had a history of asthma and all had normal lung function (mean FEV₁ 103.4% predicted). All patients had a positive skin prick test to grass pollens. Six patients also had a positive skin prick test to tree pollen, and 11 patients had a positive reaction to weed pollen. No patient had received oral corticosteroids or antibiotics for 6 months prior to the study. All patients were non-smokers and had normal full blood count, biochemical profile and urinalysis. Approval for the study was obtained from the Tayside Medical Ethics Committee and all patients gave their written informed consent.

Methods

The study was of a randomized placebo controlled, single-blind, double dummy, cross-over design. Patients were enrolled during June and July 1999 when grass pollen levels are typically high in Tayside. Patients were randomized to receive the following for 2 weeks, all given once daily at 08.00 h: (A) 200 µg intranasal aqueous mometasone furoate (as Nasonex, Schering-Plough, Herts, UK, two squirts of 50 µg in each nostril) plus placebo tablets; or (B) 10 mg oral montelukast (as Singulair™, Merck Sharp & Dohme Ltd, Herts, UK) and 10 mg oral cetirizine (as Zirtek, UCB Pharma, Watford, Herts, UK) plus placebo nasal spray. Prior to each treatment, and at cross-over, patients had a 1-week washout period with placebo nasal spray (two squirts in each nostril) and placebo tablets all taken at 08.00.

The nasal sprays were masked and sealed in envelopes by a pharmacist along with instruction sheets at the beginning of the trial. All treatments were dispensed by a third party. Prior to the study and at each visit, subjects were given detailed tuition in how to use their nasal sprays. Each subject received a written instruction sheet based on manufacturers' recommendations to follow while taking their medication at home, and a simple tick chart was used as an aide to compliance. Data from patients with more than 90% compliance were considered to be evaluable. The nasal sprays were primed according to manufacturers' instructions.

Measurements

Nasal nitric oxide

Patients had a measurement of nasal nitric oxide using a integrated, LR2000 clinical, real-time, nitric oxide gas analyser with an accuracy of 2ppb NO and a response time of 2 s (Logan Research, Rochester, UK) using the

procedures described by Kharitonov et al. [19]. Measurements were made during breath-holding as assessed by simultaneous measurement of exhaled carbon dioxide [20]. Three measures of nitric oxide were taken and the results were analysed as the mean of the three values. The analyser was calibrated weekly using a cylinder of nitric oxide at concentration of 108ppb.

Rhinomanometry

Patients had measurements of nasal resistance by posterior rhinomanometry using a NR6 rhinomanometer (GM Instruments, Ashgrove, Kilwinning, UK) with on-line computerized integration of total nasal flow and pressure change. Total nasal flow was measured with patients breathing tidal volumes using a face mask with their mouth closed. Nasal pressure was measured by placing a pressure probe in the patients' mouths with their soft palates open to represent posterior nasal pressure changes. Flow rates were calculated at a nasal pressure of 150 Pa. The pressure transducer and flow meter were calibrated weekly.

Acoustic rhinometry

Acoustic rhinometry was measured using a AI Executive acoustic rhinometer (GM Instruments, Ashgrove, Kilwinning, UK). A probe was inserted 0.5 cm into each nostril such that a seal was formed without distorting the nasal architecture. Patients were asked to hold their breath during the procedure. Measurements were made of volume of nasal cavity between 0 and 5 cm from the nasal orifice and similarly the cross-sectional area at 6.4 cm in both nostrils. For statistical purposes the total volume or area was taken to be the sum of the measurements from the right and left nostrils.

Diary card data

Nasal peak flow Nasal inspiratory flow rate was measured using an In-check™ flow meter (Clement Clarke International Ltd, Harlow, UK). After blowing their nose, patients inspired forcefully from residual volume to total lung capacity with their mouth closed. All measurements were made while in the sitting position with a good seal around a purpose-built face-mask. With the use of an independent adapter, patients also recorded their peak oral inspiratory flow using the same device. Both measurements were made at the same time each day, at 08.00, throughout the study and patients recorded the highest of three readings. The nasal oral index was calculated as the ratio of the peak nasal inspiratory flow to peak oral inspiratory flow.

Symptoms Patients recorded their seasonal allergic rhinitis

symptoms under nasal symptoms such as 'runny nose', 'blocked/stuffy nose', 'itchy nose', 'sneezing', and under eye symptoms such as 'itchy eyes', 'watery eyes', 'red eyes' in the evening. All symptoms were documented according to a four-point scale with zero indicating no symptoms and three indicating severe symptoms. Patients were also asked to record how much their symptoms were interfering with their daily activity on an 11-point scale, with zero representing no symptoms and 10 representing maximal symptoms. For statistical analysis the sum of nasal symptoms was analysed (total nasal symptoms) as well as the blockage (nasal blockage) and itchy (nasal itch) components.

Skin prick testing

Patients withheld antihistamine medication for 4 days prior to skin prick testing. This was performed following a standard protocol (Bencard testing solutions, Welwyn Garden City, UK) using extracts including grass, tree and weed pollen in addition to a negative control. Results were read after 10 min, a positive reaction being defined as a minimum weal diameter of 3–5 mm with erythema.

Pollen count measurement

Data were collected locally (Scottish Crop Research Institute, Dundee, UK) using a 7-day recording volumetric spore trap (Burkard Manufacturing Co. Ltd, Rickmansworth, Hertfordshire, UK) (Fig. 1).

Blood and urine measures

Subjects collected all urine from 22.00 hours the night preceding each visit until 08.00 hours on the day of each visit. The volume of each sample was recorded and aliquots were kept for analysis of cortisol and creatinine at the end of the study [21]. Patients also gave a sample of venous blood at each visit for measurement of peripheral blood eosinophil count [22].

Statistical analysis

The study was powered at the 80% level to detect a 20% change in nasal peak inspiratory flow rate [23]. For all domiciliary diary and pollen data, mean values for the 7-day placebo periods and for the last 7 days of active treatment period were analysed. Daily tree, grass and weed pollen count data were summated to provide a daily pollen score for each day of the study.

Overall comparisons between active treatments and placebos were made by multifactorial analysis of variance using subject, treatment and period as factors. Having first shown no differences between placebo prior to each active

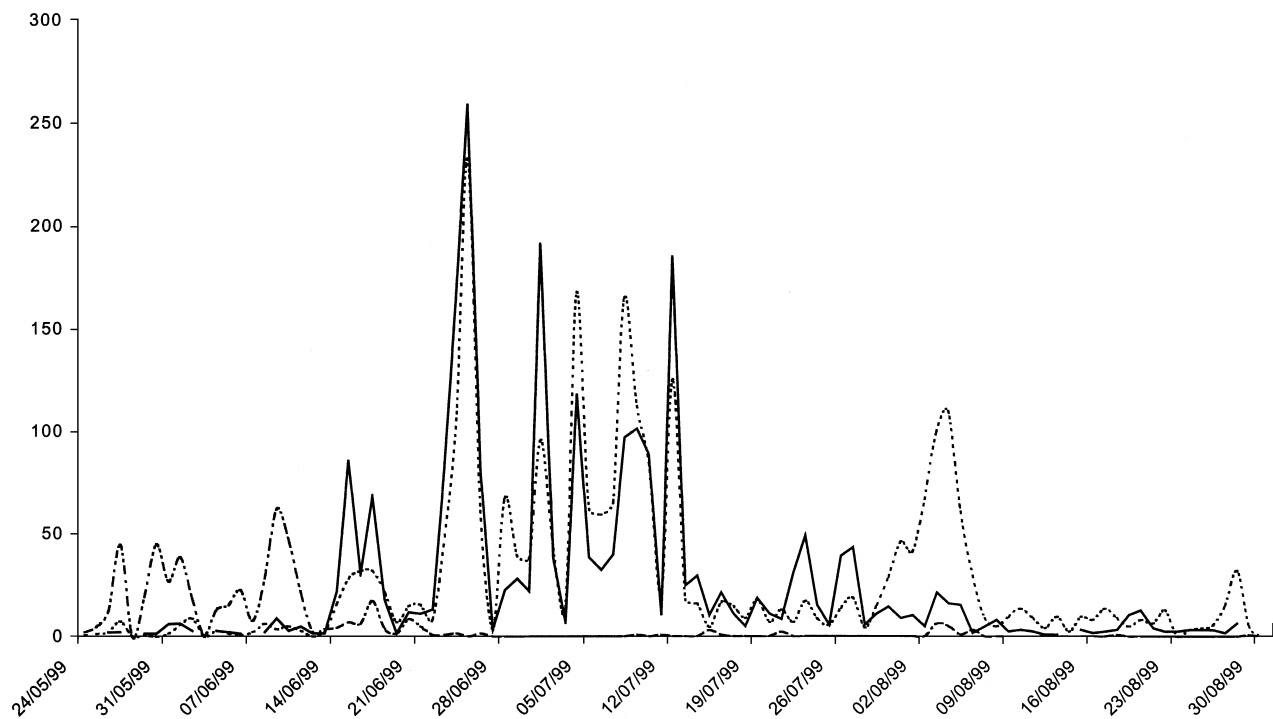


Fig. 1. Pollen counts for mixed tree, grass and weed pollens (per m³) for the local area of the study from 25 May 1999 to 24 August 1999. Chain dotted line represents tree pollen, solid line represents grass pollen and dashed line represents weed pollen.

treatment, subsequent comparisons were made using a pooled placebo and absolute values. Analysis of covariance was used to account for any influence of pollen level on treatment response. This was followed by Bonferroni's multiple range testing (set at 95% CI) in order to obviate multiple pair-wise comparisons. Consequently comparisons are only denoted as being significant ($P < 0.05$, 2 tailed) or not significant in order to not confound the alpha error. The analysis was performed using the Statgraphics statistical software package (STSC Software Publishing Group, Rockville, MD, USA).

Results

There were no significant carry-over effects between placebo values prior to each treatment for any of the endpoints (Table 1). Consequently all comparisons were subsequently made compared to a pooled placebo.

Domiciliary measures

There was significant ($P < 0.05$) improvement in domiciliary measures with both treatments compared to pooled placebo in terms of nasal peak expiratory flow rate, nasal oral index, nasal symptoms, nasal itch and blockage, eye symptoms and daily activity score (Fig. 2, Fig. 3, Table 2).

There were no significant differences between the two active treatments.

Laboratory measures

There were no significant differences with either treatment compared to pooled placebo for exhaled nitric oxide, nasal airway resistance measured by rhinomanometry, or acoustic rhinometry, in terms of the volume between 0 and 5 cm or the area at 6.4 cm (Table 2). There were no significant differences between the two active treatments.

Compared to placebo, there was no significant suppression of blood eosinophil count or overnight urinary cortisol excretion before or after correction with creatinine with either treatment (Table 2). There were no significant differences between the two active treatments. No patient reported any significant adverse effect with either of the treatment regimes.

Discussion

We have shown that monotherapy with intranasal mometasone furoate or combined histamine and leukotriene mediator antagonism with montelukast and cetirizine both resulted in significant improvements in objective and subjective domiciliary assessments of disease activity in seasonal allergic rhinitis. However, there were no significant

Table 1. Mean (SEM) values for all parameters for the placebo prior to mometasone furoate (MF) or montelukast plus cetirizine (ML + CZ). There were no significant differences between the placebo values

	PL prior to MF	PL prior to ML + CZ		PL prior to MF	PL prior to ML + CZ
Nasal nitric oxide (p.p.b.)	867 (53)	846 (52)	Nasal peak inspiratory flow (L/min)	110 (5)	112 (5)
Rhinomanometry (Pa/cm ³ /sec)	0.40 (0.07)	0.35 (0.07)	Nasal oral index (units)	0.73 (0.03)	0.74 (0.03)
Acoustic rhinometry 0–5 cm (cm ³)	21.8 (1.4)	20.2 (1.4)	Total nasal symptoms (units)	4.1 (0.3)	3.1 (0.3)
Acoustic rhinometry 6.4 cm (cm ²)	12.5 (0.9)	11.5 (0.9)	Nasal blockage (units)	1.3 (0.1)	0.9 (0.1)
Blood eosinophil count (x10 ⁹ /L)	0.31 (0.02)	0.29 (0.02)	Nasal itch (units)	1.9 (0.2)	1.5 (0.2)
Overnight urinary cortisol (nmol/10 h)	26.1 (2.9)	26.7 (2.7)	Eye symptoms (units)	2.2 (0.2)	1.6 (0.2)
Overnight urinary cortisol/creatinine ratio (nmol/mmol)	7.4 (0.8)	7.5 (0.8)	Daily activity score (units)	2.3 (0.3)	1.7 (0.3)

detectable effects in terms of nasal airways resistance or geometry as measured by rhinomanometry or acoustic rhinometry, respectively. This highlights the importance of repeated daily measures when monitoring upper airway inflammation rather than relying on laboratory data and is

perhaps analogous to the situation in asthma where several daily peak expiratory flow measurements provide a more sensitive outcome measure than a snapshot spirometry measurement in the laboratory. Integrated daily measures are likely to be more representative of disease control than

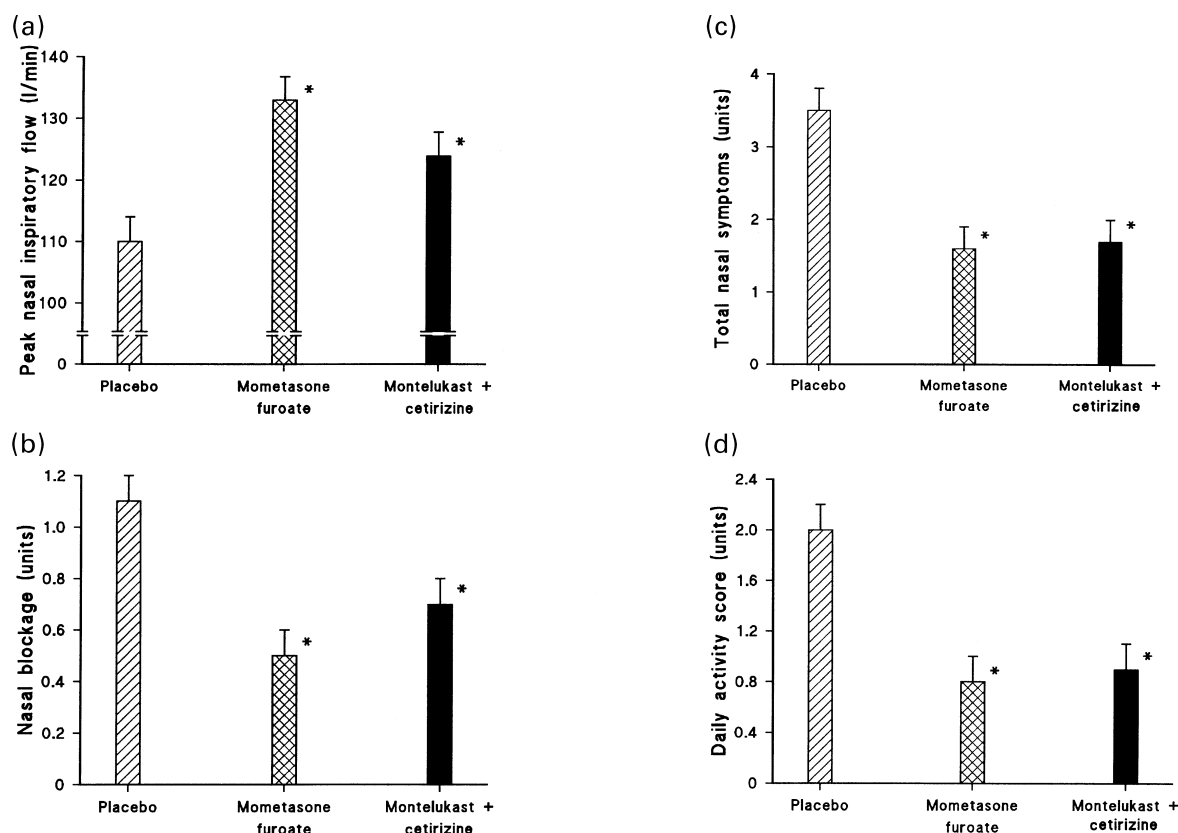


Fig. 2. (a) Peak nasal inspiratory flow, (b) nasal blockage score, (c) total nasal symptoms and (d) daily activity score, for intranasal mometasone furoate and oral montelukast plus cetirizine (montelukast + cetirizine). Data are shown as means (SEM) factored for pollen as a covariate. Asterix denotes significant ($P < 0.05$) difference between active treatment and pooled placebo.

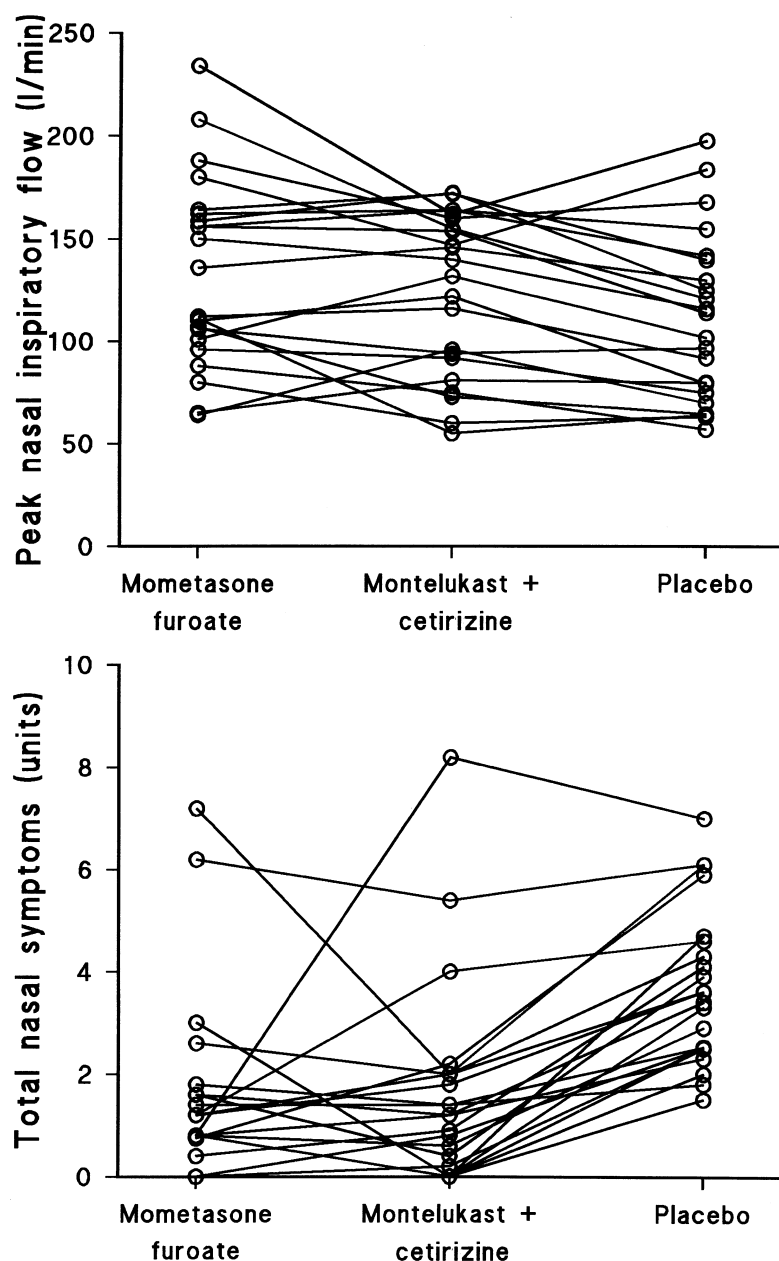


Fig. 3. Scatter plots for (a) peak nasal inspiratory flow and (b) total nasal symptoms. Solid line joins the data for an individual patient.

an isolated evaluation, as both asthma and rhinitis disease severity varies either spontaneously or in response to allergen exposure and treatment.

Previous work has confirmed the superiority of intranasal corticosteroids when compared to monotherapy with histamine or leukotriene antagonists [9, 23]. However, the combined use of montelukast and cetirizine demonstrated a significant improvement compared to placebo which was comparable to intranasal mometasone furoate. In terms of symptomatic response, the nasal symptom scores or nasal blockage profile were reduced by 50% with either treatment regimen when compared to placebo. The effect of

combined mediator blockade on nasal blockage is interesting as antihistamine alone tends to be less effective for this symptom [14], perhaps reflecting the additional effect of combined treatment on the late allergic response [18]. We chose mometasone furoate as it is an example of a highly potent corticosteroid [24] and we were also careful to ensure that the patients used their nasal spray correctly. Montelukast and cetirizine are both potent receptor antagonists of leukotriene D₄ and histamine, respectively, and are licensed for a once-daily treatment regime. Although the treatment period was relatively short, in order to ensure the crossover study was conducted during

Table 2. Means with SEM for laboratory and domiciliary measures. Asterisk denotes significant difference from pooled placebo for either active treatment

	Pooled Placebo	Mometasone furoate	Montelukast plus cetirizine
Nasal nitric oxide (p.p.b.)	855.1 (41.2)	788.0 (41.6)	856.0 (43.7)
Rhinomanometry (Pa/cm ³ /sec)	0.38 (0.04)	0.26 (0.04)	0.29 (0.05)
Acoustic rhinometry	20.9 (0.8)	19.1 (0.9)	18.1 (1.0)
Volume 0–5 cm (cm ³)			
Acoustic rhinometry	12.0 (0.6)	11.0 (0.6)	10.5 (0.7)
Area at 6.4 cm (cm ²)			
Overnight urinary cortisol (nmol/10 h)	26.3 (2.3)	29.3 (2.5)	24.0 (2.5)
Urinary cortisol creatinine (nmol/mmol)	7.5 (0.6)	7.9 (0.6)	7.7 (0.6)
Blood eosinophil count (x10 ⁹ /L)	0.31 (0.02)	0.25 (0.02)	0.27 (0.02)
Nasal oral index (units)	0.72 (0.02)	0.85 (0.02)*	0.81 (0.02)*
Nasal itch (units)	1.7 (0.1)	0.8 (0.1)	0.7 (0.1)
Eye symptoms (units)	1.9 (0.2)	0.9 (0.2)*	0.7 (0.2)*

peak pollen levels, 2 weeks of treatment has been shown to be sufficient for a maximal response with intranasal corticosteroids, and histamine and leukotriene receptor antagonists [25–27].

Domiciliary nasal peak inspiratory flow rate, which has been shown to correlate significantly with symptoms of allergic rhinitis [23], is a product of both nasal patency and lower airways inspiratory effort. To correct for pulmonary function, a nasal/oral index, the ratio of nasal and oral flow, has been developed and validated in patients undergoing surgery, both as ratio of forced inspiratory volume in one second [28] and peak inspiratory flow rate [29]. Even in patients with normal lung function or mild airflow limitation, the nasal oral index may be a useful tool as, by compensating for lung function, it may be used without reference to patients' height, age or sex.

Our results with mometasone furoate, in terms of having no detectable effects on systemic activity markers (i.e. urinary cortisol excretion), are in keeping with previous data where no significant adrenal suppression was found in terms of 24-h serum and urinary cortisol measures with mometasone [22]. We utilized overnight urinary cortisol with and without correction for creatinine excretion which has been shown to be as sensitive as a full 24-h urinary collection and more sensitive than morning serum cortisol suppression [30]. The lack of suppression of blood eosinophil count with mometasone furoate 200 µg per day has also been previously documented [22]. Previous asthma studies have shown that the significant anti-eosinophilic effects of oral leukotriene receptor antagonists are observed only after several weeks of treatment and therefore it is not surprising that no effects were seen in our study, as each treatment phase was only for 2 weeks [31].

In conclusion we have found combined mediator

blockade with cetirizine and montelukast to afford equivalent objective and subjective clinical efficacy as intranasal mometasone furoate. Furthermore, domiciliary measures of nasal peak inspiratory flow were better objective markers of allergic rhinitis than more complex assessment in the laboratory.

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